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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, Maryland 20850

FEB 19 2002

WARNING LETTER

VIA FEDERAL EXPRESS

Bernard R. Cope
Regulatory Affairs Manager
Biomet Merck Limited
Waterton Industrial Estate
Bridgend, South Wales
CF31 3XA, United Kingdom

Dear Mr. Cope:

We are writing to you because on September 13, 2001, an investigator from the Food and Drug Administration (FDA) collected information that revealed serious regulatory problems involving your implantable orthopedic prosthesis devices.

Under a United States (U.S.) Federal law, the Federal Food, Drug, and Cosmetic Act (the Act), these products are considered medical devices because they are used to diagnose or treat a medical condition or to affect the structure or function of the body (Section 201(h) of the Act).

The above-stated inspection revealed that the methods used in, or the facilities or controls used for, manufacturing, packing, storage, or installation of these devices are not in conformance with the Quality System Regulation, as specified in Title 21, Code of Federal Regulations (CFR), Part 820. In legal terms, the products are adulterated within the meaning of section 501(h) of the Act, as follows:

1. **Failure to validate with a high degree of assurance a process that cannot be fully verified by subsequent inspection and test as required by 21 CFR 820.75(a).** For example:

   a. The sterilization process used for distributed manufactured product has not been adequately validated because of the failure to relate simulated product to actual product. Specifically, bioburden on the simulated product does not represent bioburden of the manufactured product because the simulated product (metal disks about 0.5 by 1.5 inches) did not go through the routine manufacturing processes used for actual product. Also, the size of the simulated product is not similar to actual product, thereby possibly affecting the dose distribution and the locations of minimum dose in the load.

Your response of September 25, 2001, stated that in the future you will manufacture the simulated product from raw materials every time you carry out a dose audit, so that they go through every stage of the process. You stated that you are half-way through a quarterly dose audit and when that is completed the next one will be done using new manufactured simulated product, as will all future dose audits.

You stated further that your procedure BQS 1142, issue 3, "Validation of the Gamma Irradiation Sterilization Process," dated July 1999, has been updated to reflect these changes and you included copies of the previous and current procedures. You stated that the new procedure has not yet been signed by all the signatories because you wanted to respond quickly.

Your response is not adequate. The procedure has not been approved and has not been applied to a validation of the product.

b. The testing procedure used for determining bioburden has not been validated in that the recovery rate of the test has not been determined. Therefore, the bioburden levels used in determining the verification dose may be underestimated.

c. The blister sealing process that seals the current sterile barrier packaging of the Stanmore hip implants has not been validated.

Your response of September 25, 2001, stated that the design of the current blister/lid combination is different than the previously validated design, although it is also similar in that it is a PETg blister, heat sealed with a Tyvek® lid. You stated that the seal strength specification remains the same and burst tests are carried out on samples from every production run and that you are confident that the sterile seals are satisfactory. You stated that you will validate the Nelipak blister sealing process to your established protocols and that this will take three months to fully complete. You included a copy of your package validation protocol.

This response is not adequate since the procedure(s) submitted is not a complete validation of the packaging process.

2. **Failure to establish and maintain procedures for monitoring and control of process parameters for validated processes to ensure that the specified requirements continue to be met as required by 21 CFR 820.75(b)**. For example, the Nelipak sealer settings for each lot or batch of devices sealed through the Nelipak blister sealing process have not been documented.

Your response of September 25, 2001, stated that prior to every packaging run, you run off empty blisters and check the seals by carrying out burst tests, peelability tests and visual inspection and that the results of these tests are recorded. You stated that the investigator stated that you should also be recording the sealing parameters; i.e., time, temperature and pressure. You state that Process Specification PS No. 75, Issue G, has been amended to include a requirement to record the sealing parameters at the time the tests were taken.

Copies of the revised process specification and the modified record sheet were included with your response.

This response appears to be adequate, but its implementation must be verified during the next inspection.

3. **Failure to investigate the cause of nonconformities relating to product, processes and the quality system in accordance with 21 CFR 820.100(a)(2).** For example, there is no documentation that an adequate failure investigation was performed after the December 2000 dose audit revealed nine positive sterility samples. The next revalidation in January/February 2001 also found nine positive sterility samples, and there is no documentation that a failure investigation was conducted to determine the causes of the failures

Your response of September 25, 2001, stated that this is now a historical event and there is nothing you can do about it, except to learn from it and to take action to prevent similar situations from occurring in the future. You stated you have carried out a retrospective failure investigation in order to document the things you reviewed at that time and stated you have added a new clause, "Corrective Action," to your procedure BQS 1142, "Validation of the Gamma Irradiation Sterilization Process," dated July 1999, that defines the actions to be taken in the event of a dose audit/revalidation failure and the need for a documented failure investigation. You stated you will abide by this clause in the future and you included a copy of the revised procedure, BQS 1142, dated September 2001.

This response is adequate in part. However, it does not address the underlying concern that the sterilization process has not been validated (21 CFR 820.75), or provide assurances that product which has been distributed is sterile.

4. **Failure to identify the action(s) needed to correct and prevent recurrence of non-conforming product and other quality problems in accordance with 21 CFR 820.100(a)(3).** For example, the sterilization process was not validated as required by the firm's procedures after the December 2000, dose audit revealed nine positive sterility samples. The next revalidation in January/February 2001, also found nine positive sterility samples, and there is no documentation that a failure investigation was conducted to determine the causes of the failures. The firm did not evaluate the product in the field.

Your response of September 25, 2001, stated that this is now a historical event and there is nothing you can do about it, except to learn from it and to take action to prevent similar situations from occurring in the future. You stated you have carried out a retrospective failure investigation in order to document the things you reviewed at that time and stated you have added a new clause, "Corrective Action," to your procedure BQS 1142, Issue 3, "Validation of the Gamma Irradiation Sterilization Process," dated July 1999, that defines the actions to be taken in the event of a dose audit/revalidation failure and the need for a documented failure investigation. You stated you will abide by this clause in the future. You included a copy of the revised procedure, BQS 1142, Issue 4, dated September 2001.

This response is not adequate because you did not follow your existing procedures for addressing sterilization failures by validating the sterilization process.

This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Act and regulations. The specific violations noted in this letter and in the FDA 483 issued at the closeout of the inspection may be symptomatic of serious underlying problems in your firm's manufacturing and quality assurance systems. You are responsible for investigating and determining the causes of the violations identified by the FDA. If the causes are determined to be systems problems, you must promptly initiate permanent corrective actions.

We acknowledge that you have submitted to this office a response dated September 25, 2001, concerning our investigator's observations noted on the form FDA 483. We have reviewed your response and concluded that it is inadequate. An evaluation of specific responses is entered after each one of the deviations listed above.

Given the serious nature of these violations of the Act, your implantable orthopedic prosthesis devices may be detained without physical examination upon entry into the United States until these violations are corrected.

In order to remove the devices from this detention, it will be necessary for you to provide a written response to the charges in this Warning Letter for our review. After we notify you that the response is adequate, it will be your responsibility to schedule an inspection of your facility. As soon as the inspection has taken place, the implementation of your corrections have been verified, and you are notified that your corrections are adequate, your devices may resume entry into this country.

Federal agencies are advised of the issuance of all Warning Letters about devices so that they may take this information into account when considering the award of contracts. Also, no requests for Certificates for Products for Export will be approved until the violations related to the subject devices have been corrected.

Please notify this office in writing, within 15 working days of receipt of this letter, of the specific steps you have taken to correct the noted violations. Include an explanation of each step being taken to identify and make corrections to any underlying systems problems necessary to assure that similar violations will not recur. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your response should be sent to:

James W. Eisele, Consumer Safety Officer
CDRH/Office of Compliance
Division of Enforcement III (HFZ-343)
2094 Gaither Rd.
Rockville, MD 20850

If you have any questions about the contents of this letter, please contact Mr. Eisele at the above address or at (301) 594-4659, or fax (301) 594-4672. You may obtain general information about all of FDA's requirements for manufacturers of medical devices by contacting our Division of Small Manufacturers International and Consumer Assistance at (301) 443-6597, or through the Internet at **http://www.fda.gov**.

Sincerely yours,

Larry D. Spears
Acting Director
Office of Compliance
Center for Devices and
Radiological Health